REMARKS

Claims 2, 40, and 41 have been amended to correct antecedent problems contained therein. Therefore, the amendments to the claims do not raise new issues or present new matter. Claims 8-38 were canceled, and claim 39 has been withdrawn as being directed to a non-elected invention. Therefore, claims 1-7 and 40-41 are pending in the captioned application. Entrance of the amendments and further examination and reconsideration of claims 1-7 and 40-41 are respectfully requested.

Defective Oath or Declaration

The Office Action states that "The oath or declaration is defective because: for inventor Mark Chandler, the signature does not include a date of signing." (Office Action – page 2). In compliance with 37 CFR 1.67(a), Applicant attempted to procure the signature and date on a corrected Declaration from Mark Chandler. Attached hereto is a Petition and Statement of Facts to support that Mark Chandler refuses to sign such corrected Declaration.

Priority Claim Under 35 U.S.C. 119(e)

The Office Action states that "Priority to provisional application 60/153,941 filed 15 September 1999 remains denied for the reasons set forth in the previous Office Actions." (Office Action – page 2). As set forth in detail in the Amendment; Response to Office Action mailed July 6, 2004 filed in the present case on October 6, 2004, which is incorporated by reference as if fully set forth herein, Applicant respectfully traverses this assertion. However, despite the maintained denial of the priority claim to U.S. Provisional Application Serial No. 60/153,941, Applicant believes that the present claims are in condition for allowance as set forth in more detail herein.

Section 112, second paragraph, Rejections

Claims 1-7, 40, and 41 were rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Applicant sincerely appreciates the Examiner's detailed explanation of the § 112, second paragraph, rejections provided on page 4 of the Office Action. Claim 2 has been amended to address the specific problems in this claim identified in the Office Action.

The Office Action states that "Claims 1 and 7 recite 'one reagent designed to interact selectively' with a pre-determined analyte'. It is unclear as to the metes and bounds of 'selectively' in the claims. Does selectively mean interaction with one and only one analyte, or some other meaning." (Office Action -- page 4). Claim 1 recites in part: "wherein the microspheres of the one subset are coupled to at least one reagent designed to interact selectively with a predetermined analyte." Claim 7 also recites this limitation.

The term "interact selectively" is known in the art, and the term is not assigned any special meaning in the specification. For example, the term "interact selectively" is described in the Specification on page 4, lines 1-3, page 15, lines 11-17, and page 20, line 24 to page 21, line 2. A fundamental principle contained in 35 U.S.C. 112, second paragraph is that applicants are their own lexicographers. They can define in the claims what they regard as their invention essentially in whatever terms they choose so long as any special meaning assigned to a term is clearly set forth in the specification. MPEP 2173.01.

In addition, the term "interact selectively" recited in the claims is definite when analyzed in light of the content of the particular application disclosure, the teachings of the prior art, and the claim interpretation that would be given by one possessing the ordinary level of skill in the pertinent art at the time the invention was made. The essential inquiry pertaining to this requirement is whether the claims set out and circumscribe a particular subject matter with a reasonable degree of clarity and particularity. Definiteness of claim language must be analyzed, not in a vacuum, but in light of: (A) The content of the particular application disclosure; (B) The teachings of the prior art; and (C) The claim interpretation that would be given by one possessing the ordinary level of skill in the pertinent art at the time the invention was made. MPEP 2173.02. For example, the term "interact selectively" when analyzed in light of the content of the present application disclosure sets out and circumscribes the presently claimed subject matter with a reasonable degree of clarity and particularity. In addition, the term "interact selectively" is known in the art as evidenced by the teachings of the prior art. For example, a search of the database of patents issued from 1976 to present that is available on the USPTO website indicates a number of patents that include the term "interact selectively." Examples of patents that particularly illustrate that the term "interact selectively" was known by one possessing the ordinary level of skill in the pertinent art about the time the invention was made include U.S. Patent Nos. 6,406,913 to Ullman et al., 6,537,749 to Kuimelis et al., and 6,689,887 to Kerwin et al. Therefore, based on the content of the disclosure of the present application and the teachings of the prior art, one possessing the ordinary level of skill in the pertinent art at the time the invention was made would interpret the claims, and particularly the term "interact

selectively" as recited in the claims, as clearly and particularly setting out and circumscribing a particular subject matter. As such, the recitation of the term "interact selectively" in claims 1 and 7 does not render claims 1 and 7 indefinite.

The Office Action also states that "Claims 1 and 7 now recite 'microspheres of the one subset'. There is insufficient antecedent basis on the claim for 'the one'. Which one? Clarification is requested." (Office Action – page 4). Claim 1 recites in part: "wherein the microspheres of one subset are distinguishable from those of another subset by their characteristic fluorescent signatures, and wherein the microspheres of the one subset are coupled to at least one reagent designed to interact selectively with a predetermined analyte." (emphasis added to show antecedent basis). Claim 7 recites similar limitations. Therefore, "the one subset" has sufficient antecedent basis in claims 1 and 7. As such, the recitation of "the one subset" in claims 1 and 7 does not render claims 1 and 7 indefinite.

The Office Action further states that "Claim 5 still recites 'natural product'. It is unclear as to the limitation intended by 'natural product'." (Office Action -- page 4). Claim 5 recites in part: "wherein the at least one reagent comprises a small molecule, natural product, synthetic polymer, peptide, polypeptide, polysaccharide, lipid, nucleic acid, or combinations thereof."

The term "natural product" is known in the art, and the term is not assigned any special meaning in the specification. Support for the limitations of claim 5 can be found in the Specification, for example, on page 4, lines 1-4.

In addition, the term "natural product" is definite when analyzed in light of the content of the present application disclosure, the teachings of the prior art, and the claim interpretation that would be given by one possessing the ordinary level of skill in the pertinent art at the time the invention was made. For example, the term "natural product" when analyzed in light of the content of the present application disclosure sets out and circumscribes a particular subject matter with a reasonable degree of clarity and particularity. In addition, the term "natural product" is known in the art as evidenced by the teachings of the prior art. For example, a search of the database of patents issued from 1976 to present that is available on the USPTO website indicates at least 5152 patents that include the term "natural product." Examples of patents that particularly illustrate that the term "natural product" was known by one possessing the ordinary level of skill in the pertinent art about the time the invention was made include U.S. Patent Nos. 6,607,921 to Hindsgaul et al. and 6,693,178 to Buchwald et al. Therefore, based on the content of the

disclosure of the present application and the teachings of the prior art, one possessing the ordinary level of skill in the pertinent art at the time the invention was made would interpret the claims, and particularly the term "natural product" as recited in the claims, as clearly and particularly setting out and circumscribing a particular subject matter.

The Office Action also states that "This does not clarify what natural product is intended." (Office Action -- page 4). Therefore, the Examiner appears to equate breadth of a claim with indefiniteness. However, a claim cannot be rejected as indefinite simply because it is broad in scope. Breadth of a claim is not to be equated with indefiniteness. *In re Miller*, 441 F.2d 689, 169 USPQ 597 (CCPA 1971). MPEP 2173.04. In addition, since the scope of the subject matter embraced by claim 5 is clear for at least the reasons set forth above, and since Applicants have not otherwise indicated that they intend the invention recited in claim 5 to be of a scope different from that defined in the claims, claim 5 complies with 35 U.S.C. 112, second paragraph. If the scope of the subject matter embraced by the claims is clear, and if applicants have not otherwise indicated that they intend the invention to be of a scope different from that defined in the claims, then the claims comply with 35 U.S.C. 112, second paragraph. MPEP 2173.04. As such, the recitation of the term "natural product" in claim 5 does not render claim 5 indefinite.

For at least the reasons set forth above, claims 1-7, 40, and 41 are definite since these claims particularly point out and distinctly claim the subject matter which applicant regards as the invention. As such, removal of the § 112, second paragraph, rejections of claims 1-7, 40, and 41 is respectfully requested.

Section 103(a) Rejections

Claims 1-7, 40, and 41 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Kettman et al. (Cytometry (1998) 33:234-243) (hereinafter "Kettman") in view of Ekins (Journal of Pharmaceutical and Biomedical Analysis (1989) 7: 155-168) (hereinafter "Ekins"). As will be set forth in more detail below, the §103(a) rejections of claims 1-7, 40, and 41 are respectfully traversed.

The Examiner has failed to establish a *prima facie* case of obviousness. In particular, there is no suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art to combine Kettman and Ekins as suggested in the Office Action.

For instance, Kettman discloses an assay that is performed using up to 64 multiplexed microsphere sets. In particular, Kettman states that "In the parameters used for designing microspheres to be used for multiplexing, uniformity (low CV) is an important issue. The more uniform the population, the more sets that can be blended and used in the same mixture." (Kettman -- page 239, col. 1 to col. 2). Therefore, Kettman discloses that the number of microsphere sets that can be used in a multiplexed array are limited by the uniformity of the microspheres. In addition, Kettman states that "The median MFI of the population (Fl 2 and Fl 3) should be placed as close to the center of the classification criteria as possible. Microspheres from one set do not fall into the classification criteria for a neighboring set of microspheres. This feature is related to the uniformity of the fluorescence among the members of each microsphere set, that is, the CV." (Kettman -- page 239, col. 2). Therefore, Kettman teaches that the number of microsphere sets that can be used in a multiplexed array are limited by the fluorescence uniformity among the microsphere members of each set.

Kettman also discloses how fluorescence is imparted to the microspheres. For instance, Kettman states that "Several observations have been made regarding the use of dyes dissolved in the microspheres. Because the dyes are inside the microspheres, solvent conditions will not affect the dye characteristics." (Kettman -- page 241, col. 1). Therefore Kettman teaches that the fluorescence that is used to determine the set to which a microsphere belongs is generated by excitation of dyes located inside the microspheres. In addition, Kettman states that "Although the microsphere population is reasonably uniform, small differences in size and or composition alter the relative dyeing efficiency. Additionally, as the dye content is increased, the spectrum of the combination of two dyes changes." Therefore, Kettman teaches that variables that may affect the fluorescence, which is used to determine the set to which a microsphere belongs, include variations in the microspheres themselves and the dye content within the microspheres. Consequently, Kettman teaches that the number of microsphere sets that can be included in an assay are limited at least in part by the variations in the microspheres themselves and the dye content within the microspheres. Such limitations in the number of microsphere sets that can be used in an assay is perhaps why Kettman states that "This measurement system can analyze up to 64 analytes in a single sample." (Kettman -- abstract, col. 1, emphasis added).

In contrast, Ekins discloses a multi-analyte immunoassay that utilizes antibody molecules attached to a solid support. In particular, Ekins states that "exposure of a small number of antibody molecules (in the form, for example, of a 'microspot' located on a solid support) to an analyte-containing fluid results in an antibody binding site occupancy which reflects the analyte concentration in the medium." (Ekins --

page 166). In addition, Ekins also states that "an estimate of binding site occupancy of the 'sampling' (solid-phase) antibody may be derived by measurement of the ratio of signals emitted by the two antibodies forming the dual antibody 'couplets'. This can be conveniently achieved by labeling each of the antibodies used with different markers; for example, a pair of radioactive, enzyme or chemiluminescent markers." (Ekins -- page 166). Therefore, Ekins teaches that the labels that are used to distinguish one antibody from another are coupled to the antibodies themselves.

Consequently, unlike the assay of Kettman in which the fluorescent markers are dissolved within the solid substrate (e.g., microspheres), the markers used by Ekins are not dissolved or otherwise integrated into a solid substrate. In particular, as shown in Figure 6 of Ekins, in an immunoassay that relies on fluorescent labeled antibodies, the fluorescent label that emits the ß fluorophore is attached to antibodies, and the antibodies are attached to the solid substrate. Therefore, the fluorescent markers of Ekins are external to the solid substrate. In addition, Ekins states that "The concept is also being exploited in the development of 'multi-analyte' immunoassay systems, enabling the simultaneous measurement of tens or even hundreds of substances simultaneously in the same small sample." (Ekins, Abstract, page 155). Therefore, unlike the assays of Kettman, which as taught by Kettman are limited at least in part by the variations in the microspheres themselves and the dye content within the microspheres, Ekins appears to teach that using fluorescently labeled antibodies located externally to a solid substrate in an assay does not limit the assay to measuring up to 64 analyte in one sample.

As set forth in detail above, therefore, the assay of Kettman uses fluorescent labels dissolved in microspheres while the assay of Ekins uses fluorescent labels attached to antibodies located on a surface of a solid substrate. Therefore, Kettman and Ekins rely on completely different technologies to create an assay. As such, the configuration of the assays of Kettman and Ekins differs dramatically. In particular, the assays of Kettman and Ekins use dramatically different technologies for fluorescently-labeling the probes of the assays. In addition, as known by one possessing the ordinary level of skill in the art at the time the invention was made, the technology for coupling fluorescent labels to antibodies cannot be used to incorporate fluorescent labels into a microsphere. Therefore, there is no suggestion or motivation to combine elements of the assays taught by Kettman and Ekins. Consequently, there is no suggestion or motivation, either in Kettman, Ekins, or in the knowledge generally available to one of ordinary skill in the art, to combine the teachings of Kettman and Ekins as suggested in the Office Action. As a result, at least one of the three basic criteria for establishing a *prima facie* case of obviousness has not been met. To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some

suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). MPEP 2142.

Therefore, even if the references taught every element of the claims as contended by the Examiner, since there is no motivation to combine the teachings of the references, a rejection based on a *prima facie* case of obviousness is improper. The combination of the references taught every element of the claimed invention, however without a motivation to combine, a rejection based on a *prima facie* case of obvious was held improper. MPEP 2143.01.

Moreover, even if the fluorescent markers of Ekins could be coupled to the surface of the microspheres of Kettman, the prior art appears to teach away from such a modification of the microspheres of Kettman. In particular, Kettman appears to teach away from attaching fluorescent-based labels to a surface of the microspheres to distinguish the microspheres of one set from those of another. For instance, Kettman states that "Because the dyes are inside the microspheres, solvent conditions will not affect the dye characteristics." (Kettman -- page 241, col. 1). Therefore, according to the teachings of Kettman, if the fluorescent-based labels are attached to a surface or a reagent on a surface of the microspheres (i.e., external to the microspheres), the solvent conditions will affect the dye characteristics of the microspheres thereby decreasing the uniformity of the fluorescence of microspheres in a set. In addition, as described above, Kettman teaches that non-uniformity of fluorescence limits how many microsphere sets can be used in an assay. Therefore, Kettman teaches that attaching the fluorescent based labels of Ekins to the surface of the microspheres of Kettman will increase the non-uniformity of the fluorescent characteristics of the microspheres thereby reducing the number of microsphere sets that can be used in the assay. As such, the teachings of Kettman appear to teach away from the combination of Kettman and Ekins suggested in the Office Action. A prior art reference must be considered in its entirety, i.e., as a whole, including portions that would lead away from the claimed invention. *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984). MPEP 2141.02.

At the very least, the teachings of Kettman and Ekins conflict as to appropriate fluorescent labels for probes used to measure multiple substances in a single sample. In particular, the teachings of Kettman suggest to one of ordinary skill in the art that the fluorescent labels taught by Ekins are not suitable for labeling the microspheres taught by Kettman since, as set forth in detail above, Kettman teaches that solvent conditions may affect the dye characteristics of microspheres labeled with dyes that are external to

the microsphere substrate. In addition, as set forth in detail above, Ekins clearly teaches that the fluorescent-based labels are attached to an antibody coupled to a surface of a substrate (i.e., the labels are external to the substrate). Therefore, the teachings of Kettman appear to discredit the teachings of Ekins. In any case, the teachings of the prior art certainly do not suggest to one of ordinary skill in the art the combination of Kettman and Ekins as asserted in the Office Action. The test for obviousness is what the combined teachings of the references would have suggested to one of ordinary skill in the art, and all teachings in the prior art must be considered to the extent that they are in analogous arts. Where the teachings of two or more prior art references conflict, the examiner must weigh the power of each reference to suggest solutions to one of ordinary skill in the art, considering the degree to which one reference might accurately discredit another. *In re Young*, 927 F.2d 588, 18 USPQ2d 1089 (Fed. Cir. 1991). MPEP 2143.01.

Furthermore, even though Ekins discloses the ability of measuring "even hundreds" of substances in the same sample, for at least the reasons set forth above, there is no suggestion that the teachings of Kettman can be modified by the teachings Ekins to successfully enable measurements in a single sample of more than the 64 analytes disclosed by Kettman. For example, Ekins does not disclose that fluorescent-based labels can be dissolved into microspheres. Simply put, Ekins does not teach or suggest any method for generating fluorescently-labeled probes other than attaching fluorescent-based labels to antibodies. In addition, as taught by Kettman, the number of sets that can be used in a single mixture depends on the uniformity of the fluorescence of each member of the sets, and fluorescent dyes that are not inside the microspheres will be affected by solvent conditions thereby reducing the uniformity of the microspheres in a set. Therefore, there is no suggestion in the art that the teachings of Kettman can be combined with the teachings of Ekins as suggested in the Office Action with any reasonable expectation of increasing the number of analytes that can be measured in the assay of Kettman. Consequently, Kettman cannot be combined with Ekins to reject the present claims as *prima facie* obvious. The prior art can be modified or combined to reject claims as *prima facie* obvious as long as there is a reasonable expectation of success. *In re Merck & Co., Inc.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). MPEP 2143.02.

For at least the reasons set forth above, there is no reasonable expectation of success that the teachings of Ekins can be combined with the teachings of Kettman to create an assay that can measure more than 64 analytes in a single sample. Obviousness does not require absolute predictability, however, at least some degree of predictability is required. Evidence showing there was no reasonable expectation

of success may support a conclusion of non-obviousness. *In re Rinehart*, 531 F.2d 1048, 189 USPQ 143 (CCPA 1976). MPEP 2143.02.

For at least the reasons set forth above, the prior art does not suggest the desirability of combining the teachings of Kettman with the teachings of Ekins. Therefore, even if the teachings of Kettman and Ekins can be combined as suggested in the Office Action, the resulting combination is not obvious and is not sufficient to establish *prima facie* obviousness of the present claims. The mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. *In re Mills*, 916 F.2d 680, 16 USPQ2d 1430 (Fed. Cir. 1990). MPEP 2143.01.

Additionally, for at least the reasons set forth above, there is simply no objective reason to combine the teachings of the references as suggested in the Office Action. As such, even if modifying the teachings of Kettman with the teachings of Ekins as suggested in the Office Action would have been well within the ordinary skill of the art at the time the claimed invention was made, and if the references relied upon taught that all aspects of the claimed invention were individually known in the art, the combination of the prior art suggested in the Office Action is not sufficient to establish a *prima facie* case of obviousness. A statement that modifications of the prior art to meet the claimed invention would have been " 'well within the ordinary skill of the art at the time the claimed invention was made'" because the references relied upon teach that all aspects of the claimed invention were individually known in the art is not sufficient to establish a *prima facie* case of obviousness without some objective reason to combine the teachings of the references. *Ex parte Levengood*, 28 USPQ2d 1300 (Bd. Pat. App. & Inter. 1993). MPEP 2143.01.

Accordingly, there is simply no teaching, suggestion, or motivation to combine or modify the teachings of Kettman with the teachings of Ekins as suggested in the Office Action. Consequently, obviousness of the present claims has not been established. Obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so. *In re Bond*, 910 F.2d 81, 834, 15 USPQ2d 1566, 1568 (Fed. Cir. 1990).

For at least the reasons stated above, Ekins cannot be combined with Kettman to overcome deficiencies contained therein. As such, claims 1-7, 40, and 41 are patentably distinct over the cited art. Accordingly, removal of the § 103 rejections of claims 1-7, 40, and 41 is respectfully requested.

Notice of Change of Address

Applicant respectfully requests that all correspondence in the present case be directed to the following address:

Daffer McDaniel LLP
P.O. Box 684908
Austin, TX 78768-4908
Ph: (512) 476-1400

CONCLUSION

This response constitutes a complete response to all issues raised in the Office Action mailed December 28, 2004. In view of the remarks traversing rejections presented therein, Applicants assert that pending claims 1-7 and 40-41 are in condition for allowance. If the Examiner has any questions, comments, or suggestions, the undersigned earnestly requests a telephone conference.

The Commissioner is authorized to charge any fees, or credit any overpayment, to deposit account number 50-3268/5868-02801.

Respectfully submitted,

Ann Marie Mewherter
Reg. No. 50,484
Agent for Applicant(s)

Daffer McDaniel
P.O. Box 684908
Austin, TX 78768-4908
Ph: (512) 476-1400
Date: 3.25.05